

Preeclampsia

The following section is entitled “**Preeclampsia**”. This section familiarizes the medical provider with the diagnostic features and medical management of preeclampsia. The section begins with a *learner handout* with space for the learner to make their own notes. The *learner handout* is followed by the *teaching script* for the educator. Relevant *cases* for discussion and a *bibliography* of articles related to preeclampsia and chronic hypertension in pregnancy can be found at the end of this section.

P R E E C L A M P S I A

PREECLAMPSIA / PREGNANCY INDUCED HYPERTENSION

Incidence

- Preeclampsia complicates at least 10% of first pregnancies

Etiology

- The etiology of preeclampsia is unknown but may be related to abnormal placentation.

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Pathophysiology

- Preeclampsia most commonly presents in the second half of pregnancy.
- It is a multisystem disease associated with diffuse vasospasm and endothelial damage.

Pathophysiology

- Pathology demonstrates areas of endothelial swelling, edema, micro-infarctions and micro-hemorrhages in effected organs.

Risk Factors

- first pregnancy
- new mailings
- younger than 18 and older than 35
- prior history
- family history
- multiple gestations
- hydatidiform mole
- hydrops
- triploidy

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Risk Factors

- chronic hypertension
- diabetes
- renal disease
- SLE
- thrombophilias (especially APLA)
- obesity

Diagnosis

- Though important manifestations of the disease, hypertension, proteinuria, and edema are *not* essential to the diagnosis of preeclampsia.
- The likelihood of preeclampsia increases when more elements of the disease are present.

Symptoms

- headache
- visual disturbances
- epigastric or RUQ discomfort
- edema/rapid weight gain

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Signs

- hypertension
- retinal vasospasm
- hepatic tenderness
- facial and hand edema
- clonus

Laboratory Manifestations

- proteinuria
- elevated creatinine
- elevated uric acid
- elevated liver enzymes
- elevated hemoglobin
- thrombocytopenia
- elevated PT and PTT
- microangiopathic hemolytic anemia

Life Threatening Manifestations

- seizures
- cerebral hemorrhage
- renal failure
- hepatic failure
- liver hematoma with hepatic failure
- DIC
- pulmonary edema
- ventricular dysfunction
- placental abruption

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Fetal Effects

- Preeclampsia has significant adverse fetal effects including decreased amniotic fluid levels, decreased fetal growth, placental abruption, and intrauterine fetal demise.

Treatment

- When preeclampsia is diagnosed, it is always in the mother's interest to deliver her baby; therefore, any delay in delivery must be because of uncertainty about the diagnosis or immaturity of the fetus.

Treatment

- The use of an anticonvulsant to prevent seizures should be considered. Magnesium sulfate is most commonly used.
- Keep blood pressure below 180 systolic and 110 diastolic.
- Minimize fluids.
- Monitor patient and labs closely as status can deteriorate rapidly.

PREECLAMPSIA

Teaching Script

Preeclampsia and pregnancy induced hypertension (PIH) are often used as interchangeable terms. Some clinicians are more strict in their definitions and use the term PIH to refer to only those patients with isolated hypertension occurring during pregnancy. These clinicians reserve the term preeclampsia for pregnant women with hypertension occurring in association with manifestations such as proteinuria, edema and elevated liver enzymes.

Preeclampsia is common and complicates at least 10% of first pregnancies. It is extremely rare prior to 20 weeks gestation and the vast majority of cases occur close to term (near 38-40 weeks gestation).

Etiology

Despite extensive investigation and many proposed theories, the etiology of preeclampsia is unknown and, in fact, the entity is remarkably poorly understood. What we do know about the etiology of preeclampsia is that the process probably begins early on in gestation. This has been established from autopsy studies done on women who die with preeclampsia. In these cases it can be shown that trophoblastic implantation into the maternal endometrium did not occur in a normal fashion in women with preeclampsia. In particular, it can be seen that the interface between maternal and fetal circulatory systems is less extensive in women who develop preeclampsia than in women who do not. Many of the manifestations of preeclampsia are therefore felt to be related to a perceived ischemia of the placenta. However, much remains to be worked out as to why and how this process occurs and why this placental ischemia manifests itself in the manner that it does.

Pathophysiology

Preeclampsia is a multisystem disease that is specific to the second half of pregnancy. On a pathophysiologic level, it is characterized by diffuse vasospasm and endothelial damage. Pathology of affected organs in preeclampsia demonstrates areas of endothelial swelling, edema, micro-infarctions and micro-hemorrhages. The main target organs for preeclampsia are the brain, kidney, liver, lungs and heart.

Risk Factors

The risk factors for preeclampsia include nulliparity (first pregnancy) and it is believed (though difficult to prove) that preeclampsia is also seen more commonly in new matings, which is to say in any pregnancy with a new father. Additionally, women who use barrier contraception, have undergone donor insemination, or are egg donor recipients are also at increased risk for preeclampsia. Evidence such as this supports the thinking that an immune response to paternal antigens may play a role in the development of the disease. Other risk factors for preeclampsia include age less than 18 years and greater than 35 years. A family history of preeclampsia and a prior history of preeclampsia are recognized to be risks as well. Obstetric risk factors for preeclampsia include multiple gestations, hydatidiform moles, fetal triploidy and hydrops. Medical conditions constituting risk factors include chronic hypertension, diabetes, renal disease, and systemic lupus. Many acquired or inherited tendency to thrombosis (especially the antiphospholipid antibody syndromes) have also been associated with an increased incidence of preeclampsia. Those most recently shown to be associated with preeclampsia are resistance to activated protein C and hyperhomocysteinemia. Yet another identified risk factor is obesity.

Diagnosis

Preeclampsia is often thought to consist of the triad of hypertension, proteinuria, and edema when, in fact, no single one of these elements is essential to the diagnosis. The fact that eclamptic seizures can occur in patients without hypertension and in patients without proteinuria illustrates this. It is probably more useful to think of the diagnosis of preeclampsia as not absolutely requiring any one specific element of the disease but, rather, as a diagnosis which is increasingly likely as more manifestations of the disease are present.

Symptoms

The main symptoms of preeclampsia are **visual disturbances, headaches, epigastric discomfort, edema and rapid weight gain**. Nausea and vomiting may also occur. Headache, a major symptom of preeclampsia, is typically migrainous in nature. The visual disturbances that characterize preeclampsia are scintillations and /or scotomas. They are thought to be secondary to cerebral vasospasm. Epigastric discomfort in preeclamptic patients can be marked and may occur out of proportion to the degree of abnormalities on liver enzymes. Thirty percent of pregnant women develop edema and, therefore, it is not a reliable sign of preeclampsia. However, it is felt to be more specific if it is present in nondependent areas, such as the hands and face, or if it is associated with a rapid weight gain.

Signs

Signs of preeclampsia include **hypertension, right upper quadrant (hepatic) tenderness, retinal vasospasm, facial and hand edema and clonus**. Hypertension, defined as a sustained blood pressure greater than 140/90, is an important manifestation of preeclampsia but is not always present in all patients. Previously it was felt that a blood pressure rise of more than 30 systolic and 15 diastolic from baseline pregnancy blood pressures was abnormal but this has

recently been drawn into question. Hepatic tenderness can be dramatic. It is felt that this tenderness is due to capsular stretching from edema of the liver. We emphasize the importance of a gentle examination of the liver in the suspected preeclamptic to our residents as the edematous liver of the preeclamptic is at risk for hemorrhage and hepatic rupture. Retinal vasospasm can be seen on funduscopic examination as segmental narrowing of arterial vessels. Retinal edema (in the form of soft exudates) and hemorrhages and exudative retinal detachments can also be seen. Clonus is an important sign of central nervous system irritability in preeclampsia but should not be over diagnosed. Most pregnant women have very brisk reflexes and we do not consider the patient to have abnormal deep tendon reflexes until three beats of clonus have been demonstrated.

Laboratory Manifestations

Laboratory manifestations of preeclampsia reflect the many systems involved in the disease. **Proteinuria** (> 300mg/dL per 24 hours) is one of the major manifestations of preeclampsia and is likely due to a lesion known as glomerular endotheliosis. This same lesion also is responsible for the **elevated creatinine** seen in many preeclamptic patients. Interpretation of creatinine, however, must be done with the knowledge that the average creatinine in pregnancy is 0.5 mg/dL. A creatinine of 0.9 mg/dL is abnormal in a pregnant woman. **Hyperuricemia**, secondary to renal tubular dysfunction, is also commonly seen. Normally the uric acid in pregnancy is lower than in the non-pregnant individual so that a level greater than 5 mg/dL is considered abnormal.

Elevated liver enzymes are an important manifestation of preeclampsia.

An **elevated hemoglobin** is often seen in preeclampsia if there is no hemolysis. This is seen because despite the edema typical of preeclampsia, preeclampsia is characterized by relative

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intravascular volume depletion. The elevated hemoglobin, therefore, is a manifestation of hemoconcentration. However, it is important to note that the majority of pregnant women in the third trimester will have a hemoglobin around 10 grams per deciliter because, in normal gestation, there is a relative increase in plasma volume that is greater than the increase in red blood cell mass. Thus, the finding of a hemoglobin of 14g/dL in a pregnant woman in the third trimester can be an early marker of preeclampsia. **Thrombocytopenia** is often also seen in preeclampsia and this is felt to be secondary to consumption.

In rare cases a coagulopathy can occur in preeclampsia manifested by an elevated PT and PTT. This is due to consumption such as that seen in **disseminated intravascular coagulation (DIC)**. Thrombocytopenia and microangiopathic hemolytic anemia are also present. The PT and PTT are not generally a routine part of screening for preeclampsia but should be checked if there are elevated liver transaminases or thrombocytopenia.

Life Threatening Manifestations

The life threatening manifestations of preeclampsia that may lead to the involvement of internists are many. Seizures are the most well known manifestation of preeclampsia. In fact, the term preeclampsia literally means pre-seizure. Once a seizure has occurred, the diagnosis becomes eclampsia. These seizures can be anything from *petite mal* to Jacksonian type seizures to *grand mal* seizures. Seizures may occur postpartum and have been reported to occur as late as 7-23 days after delivery.

Cerebral hemorrhage is responsible for 50-65% of maternal deaths in preeclampsia. These cerebral hemorrhages can be unpredictable and are not necessarily due to severe elevations in blood pressure nor are they always associated with seizures.

Oliguric or anuric renal failure can occur in the setting of preeclampsia.

Hepatic failure is also possible although, when this occurs, serious consideration of the diagnosis of acute fatty liver of pregnancy needs to be made. Hepatic infarction, hemorrhage and rupture have all been reported.

As previously mentioned, disseminated intravascular coagulation and a microangiopathic hemolytic anemia can occur . The HELLP syndrome(**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) refers to a specific constellation of findings in preeclampsia which can be severe.

Pulmonary edema is another life threatening manifestation of preeclampsia. It generally occurs due to preeclampsia related ventricular dysfunction and pulmonary endothelial damage. It may be severe enough to warrant intubation or mechanical ventilation. Many of the deaths associated with preeclampsia occur in this context. Ventricular dysfunction is seen in up to one third of severe cases of preeclampsia and echocardiographic studies have suggested that both systolic dysfunction and diastolic dysfunction can occur.

Fetal Effects

Aside from these maternal manifestations, preeclampsia has significant adverse fetal effects. These include decreased fetal growth (intrauterine growth retardation or IUGR), intrauterine fetal demise (IUID), placental abruption and decreased amniotic fluid levels. Often these complications precede the maternal clinical manifestations of preeclampsia.

Management

When preeclampsia is diagnosed, it is always in the mother's interest to deliver the baby. Once delivery has occurred, the manifestations of preeclampsia generally rapidly resolve. Any

delay in delivery therefore must be because of uncertainty about the diagnosis or justified by immaturity of the fetus. The mode of delivery should be determined by obstetrical indications as induced vaginal deliveries may be done even in severe preeclampsia. Most women in whom delivery is delayed are hospitalized because the disease is unpredictable and can worsen rapidly. Some clinicians manage “mild” disease as outpatients but this can only be done safely in limited circumstances since predicting which patients will quickly develop severe disease is nearly impossible. Generally these women are placed on bedrest which, although there is no evidence to suggest it improves overall maternal or fetal outcome, it does improve blood pressure and edema. Serial preeclampsia laboratories, including 24 hour urine collections for creatinine clearance and proteinuria, as well as fetal testing are followed.

Aside from delivery, important supportive measures to take for the preeclamptic woman include the use of an anticonvulsant to prevent seizures. Magnesium is traditionally used in the United States for this purpose. Its only role in this setting is as an anticonvulsant. It has no other role in preeclampsia and is not used to treat blood pressure. Many other countries use Phenytoin (dilantin) as their anticonvulsant of choice in the setting of preeclampsia but a recent double-blinded randomized control study suggested that magnesium was more effective in preventing seizures in women with preeclampsia. If needed acutely, intravenous benzodiazepines may be given.

There is no evidence to suggest that blood pressure control tighter than 180/110 mmHg improves maternal or fetal outcome in the setting of preeclampsia. In the absence of direct end organ damage from severe hypertension, we therefore do not treat acute blood pressures less than 180/105. When there is evidence of such damage, such as retinal hemorrhages, pulmonary edema, or severe headache, it is wiser to maintain blood pressures less than 160/100. If urgent or emergent blood pressure reduction is required intravenous labetalol or intravenous hydralazine can be used. When using these medications two points should be remembered. First, a gradual

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drop in blood pressure is desirable to avoid decreases in uteroplacental perfusion. Second, preeclamptic women are often quite sensitive to these agents so that lower doses, such as 5-10 mg of hydralazine or 10-20mg of labetalol, are often adequate. Though not used as often for acute management of hypertension anymore, calcium channel blockers should be avoided if the patient is on magnesium as the combination of magnesium and a calcium channel blocker has been associated with severe hypotension in some women. Once a woman has delivered, any antihypertensive agent can be used for blood pressure control. At that point, nitroprusside is an excellent choice because of its very short half life.

It is important to minimize intravenous fluids in the patient with preeclampsia because of their propensity to pulmonary edema. It is also important to monitor the patient and their laboratory status closely as their status can deteriorate very rapidly.

Lastly, it is worth mentioning that preeclampsia can worsen or even initially present post partum. Why this is so, is difficult to explain but is less surprising when one considers that preeclampsia is a complicated disease which is associated with abnormalities in placentation. Therefore, even though preeclampsia manifests itself late in pregnancy, the disease process likely begins very early on in gestation and the entire process may not be immediately reversed by delivery.

PREECLAMPSIA

Case Discussion

Case #1

Adapted from ACP workshop syllabus

A.H. a 33-year-old black woman, G₃P₂, presented to her internist five years previously with a blood pressure of 160/100 mmHg. Evaluation failed to disclose secondary causes of hypertension and there was no evidence of cerebrovascular, cardiac or renal disease. Blood pressure was well controlled at . 125/80 mmHg with hydrochlorothiazide 50 mg/d and propranolol 80 mg bid.

She is now being seen on the above medication for ongoing management of her hypertension. She feels well and blood pressure is 135/86 mmHg. There is no evidence of end organ disease. She mentions that she has just seen her obstetrician-gynecologist who has confirmed that she is 5-6 weeks pregnant.

The patient expresses concern about the impact of her chronic hypertension on the course of her pregnancy and health of her baby. What do you tell her?

What modifications, if any, should be made in this patient's antihypertensive drug regimen and why?

In discussing the above, the patient tells you that her obstetrician has recommended low-dose aspirin therapy in order to prevent preeclampsia. She would like your opinion as to the advisability of this approach. What do you tell her?

All antihypertensive medication was withdrawn. Blood pressure remained 120-140/70-90 mmHg until 32 weeks when values increased to 145/100 mmHg.

To what do you attribute the increase in BP? What additional history, physical exam and laboratory data should be obtained to help determine the cause?

Presuming that the history, exam and laboratory tests were unremarkable, should antihypertensive drug therapy now be resumed? If so, which one?

At 36 weeks gestation the patient developed right upper quadrant pain and nausea. She was afebrile and BP was 150/105. Examination revealed marked right upper quadrant tenderness.

Laboratory evaluation reveals the following: Hematocrit 29%; WBC 9,500; platelet count 125,000; SGOT 165 U/L (2.75 ukat/L); SGPT 158 (2.63); LDH 325 U/L (5.4 ukat/L) (nl to 225 U/L, 3.75); bilirubin total=1.9 mg/dl (32 umol/L); serum creatinine 1.0 mg/dl (88 umol/L); uric acid 5.5 mg/dl (327 umol/L); urinalysis 1+ proteinuria.

What is the differential diagnosis and what tests would you do to establish the correct etiology for the current problem?

What are the maternal risks of preeclampsia and what therapy is appropriate to reduce these risks?

What fetal risks are associated with preeclampsia?

While being induced for pre-eclampsia the patient develops severe hypertension with blood pressure consistently running 200/115.

How would you evaluate and treat her at this point?

You control her blood pressure readily with intravenous hydralazine boluses and she subsequently delivers a healthy 5 lb. 6 oz. baby boy. Her blood pressure remains elevated at 160/103 on the postpartum floor.

When would you suggest the anticonvulsant be stopped?

What should be done about her blood pressure now on the floor and at discharge? The patient wishes to breastfeed. How does this affect your recommendations?

How long can the pre-eclampsia continue to effect her blood pressure?

PRECLAMPSIA

Case Discussion

Case #2

Adapted from ACP workshop syllabus

HYPERTENSION

A 30-year-old patient comes to you for a primary care establishment visit. Her insurance has changed and she has come to see you because she wants a referral to an obstetrician. She has just found out that she is pregnant and estimates that it has been approximately 8 weeks since her last menstrual period. Her only medical problem is chronic hypertension which was diagnosed 3 years ago. Her previous internist did an extensive workup to rule out an underlying cause of hypertension despite the fact that her blood pressure was reasonably easy to control and she has a strong family history of chronic hypertension. She is presently managed on Ziac® which is a combination agent of bisoprolol and hydrochlorothiazide. Her blood pressure, when you measure it in the office, is 120/70. She states that when off of antihypertensive medications her blood pressure was 170/100.

Her examination is completely normal and in particular, shows no evidence of target organ damage from hypertension or evidence for a secondary cause of hypertension.

Key Points to Review

- 1. The main risk of chronic hypertension to a pregnancy is its' association with preeclampsia which occurs in up to 20% of chronic hypertensives. There is no way to predict which chronic hypertensive will develop preeclampsia nor is there any way of preventing the development of preeclampsia. In particular, good blood pressure control during pregnancy does not decrease the risk of preeclampsia.***
- 2. Chronic hypertensive women can either come off their blood pressure medication during pregnancy (as long as their blood pressure stays less than 160/100) or remain on a medication for which there is good data to support its' use in pregnancy.***
- 3. First line antihypertensives acceptable for use in pregnancy are: Labetalol (Trandate® or Normodyne® 100 – 1200 mg po BID) or methyl dopa (Aldomet® 250-1500 mg po BID)***
Second line agents include: Pindolol (Visken 5-30 mg BID) Atenolol (Tenormin® 50-400 mg DAILY).

The ACE inhibitors and angiotensin II antagonists are contraindicated in pregnancy even though they are not teratogens.

4. *The symptoms of preeclampsia are a migraine type headaches, migraine type visual phenomena, and epigastric pain. Edema is no longer felt to be a reliable manifestation of preeclampsia.*
5. *Physical signs of preeclampsia are: 1) worsening hypertension, 2) retinal vasospasm, 3) epigastric tenderness, and 4) clonus.*
6. *“Preeclampsia labs” are a CBC, AST, uric acid, creatinine and urinalysis for protein.*
7. *Severe early preeclampsia needs investigation for underlying thrombotic tendencies or underlying renal disease.*

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HYPERTENSION / PREECLAMPSIA IN PREGNANCY

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